Neuromuscular Diseases

Introduction

The desire to move a muscle is initiated by the brain through firing of **upper motor neurons** (UMN). When an UMN fires, the action potential is propagated along the axon—from the brain to the spinal cord. The signal is sustained by the **insulating myelin** wrapped around the axon. Along the way, the signal is repeated at the **nodes of Ranvier**—exposed unmyelinated areas of the membrane with high density of sodium channels. When the UMN reaches the ventral horn of the spinal cord, it connects with a **lower motor neuron** (LMN) of the peripheral nervous system (PNS). Neurotransmitters depolarize the LMN, which transmits a signal via peripheral nerves to the neuromuscular junction. The peripheral nerve carries a bundle of both axons of motor neurons to the muscle and axons of sensory neurons from the periphery.

Similar to the UMN, the signal in the PNS is moved along the axons by repeater nodes and protected from degradation by myelin insulation provided by Schwann cells. When an action potential reaches the NMJ, it activates presynaptic calcium channels. The influx of calcium causes vesicles full of acetylcholine (ACh) to fuse with the presynaptic membrane, releasing ACh into the NMJ to activate **nicotinic acetylcholine receptors**, depolarizing the postsynaptic muscle. The action potential then propagates along the muscle to create a contraction. Disruption in this signal at any point of the pathway can prevent normal muscle contraction and/or normal sensation. The two main categories of diseases we'll discuss are demyelinating disorders and endplate disorders.

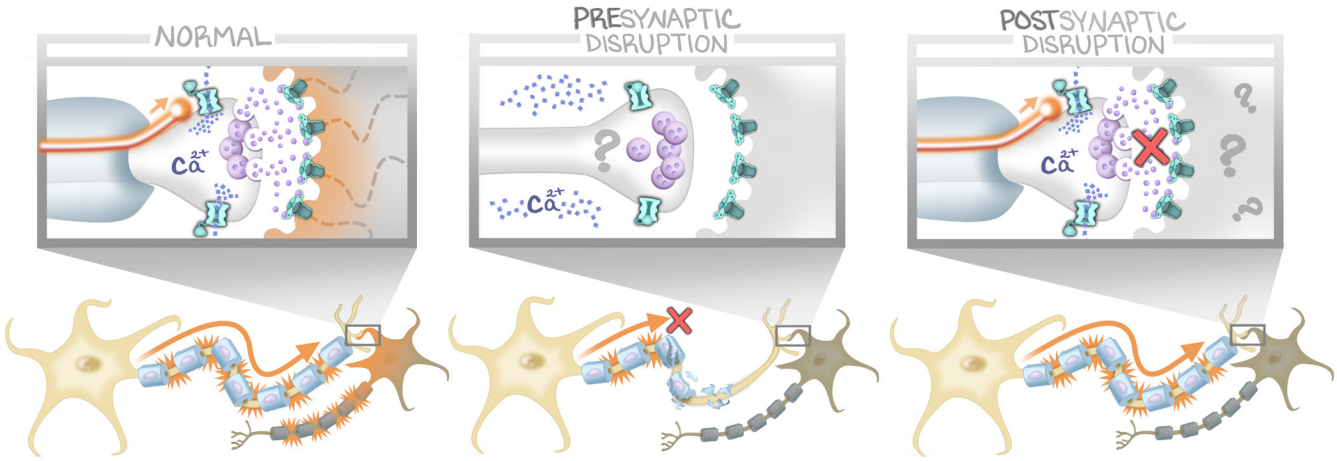


Figure 10.1: Muscle Nerve Diseases
Normal communication involves the presynaptic arrival of an action potential on a motor nerve, carried by myelinated nerve fibers with nodes of Ranvier as repeater stations, activation of presynaptic calcium channels, release of acetylcholine vesicles, and activation of postsynaptic acetylcholine receptors. In demyelination disorders, the signal never arrives at the synaptic junction: "presynaptic disruption." In neuromuscular junction disorders, antibodies impact either presynaptic calcium channels or postsynaptic acetylcholine receptors: "postsynaptic disruption."

Demyelinating disorders result from loss of the protective insulation, causing the signal to decay before it can be repeated. The transmission never makes it to its destination, the synaptic terminal. Because demyelination often encompasses a region of fibers, both **motor and sensory signals are affected**. However, due to the often more noticeable motor deficits, we tend to group the symptoms of disease based on the site of the defective motor neuron.

If a lesion is in the **central nervous system** (CNS), it's effectively the **loss of an upper motor neuron** (UMN). Upper motor neuron symptoms include **hyperreflexia**, **upgoing toes** with the Babinski reflex,

and **spastic weakness**. Demyelination of sensory fibers can lead to **variable sensory defects**. An example of a demyelinating disorder of the CNS is multiple sclerosis.

If a lesion is in the **peripheral nervous system** (PNS), it's effectively the **loss of a lower motor neuron**. Lower motor neuron symptoms include **hyporeflexia**, **no Babinski**, and **flaccid paralysis**. Because the motor and sensory fibers travel together in the peripheral nerve sheath, demyelination of that sheath will also disrupt sensory signals. Thus, these diseases cause both **motor and sensory defects**. An example of a demyelinating disorder of the PNS is Guillain-Barré.

Endplate disorders result from problems at the neuromuscular junction (NMJ). Unlike demyelinating disorders, there is not a problem in transmitting the signal to the synaptic terminal. However, when the signal arrives, either the presynaptic calcium channel is blocked, so no ACh vesicles can fuse (Lambert-Eaton) or there's something in the way of ACh binding to its receptor (myasthenia gravis). They present with **painless weakness** but **no sensory deficits**.

Multiple Sclerosis: Upper Motor Neurons

Multiple sclerosis is a **demyelinating disorder** of **upper motor neurons** (the central nervous system is affected). It is a **chronic autoimmune disease** caused by **antibodies against myelin**. The brain and spinal cord can be affected. **White women** in their 30s and 40s have the highest risk.

Acute attacks of the disease present with **sudden loss of neurologic function** corresponding to the site of the acute lesion in the brain or spinal cord. Due to the sudden loss of function, the first episode is likely to be treated like a stroke, though no stroke is found. Initial deficits from each lesion may resolve, but the disease will continue to **relapse and recur**. The diagnosis is made by finding central nervous lesions that are **anatomically separate** (no one lesion could explain all symptoms) and are **temporally distinct** (left arm last time, right foot thifs time). Because demyelination can occur anywhere, any organ can be affected.

Despite its understandably variable presentation, there are a few "classic" symptoms that are tested: **optic neuritis** (blurry vision), **vertigo** (CN VIII), **scanning speech** (sound drunk, but aren't), and **internuclear ophthalmoplegia** (loss of the medial lateral fasciculus). And yes, the hard words to say are the ones the test likes to use.

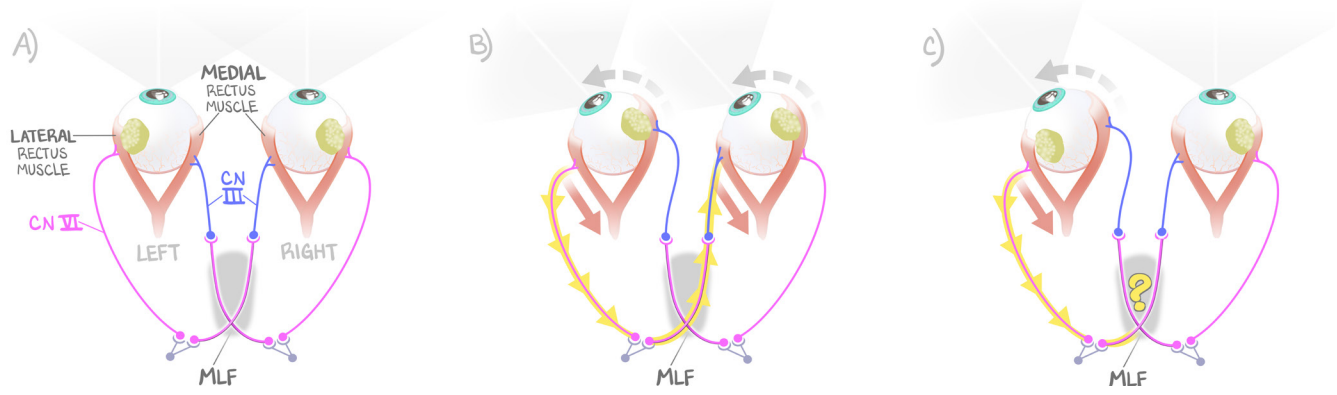
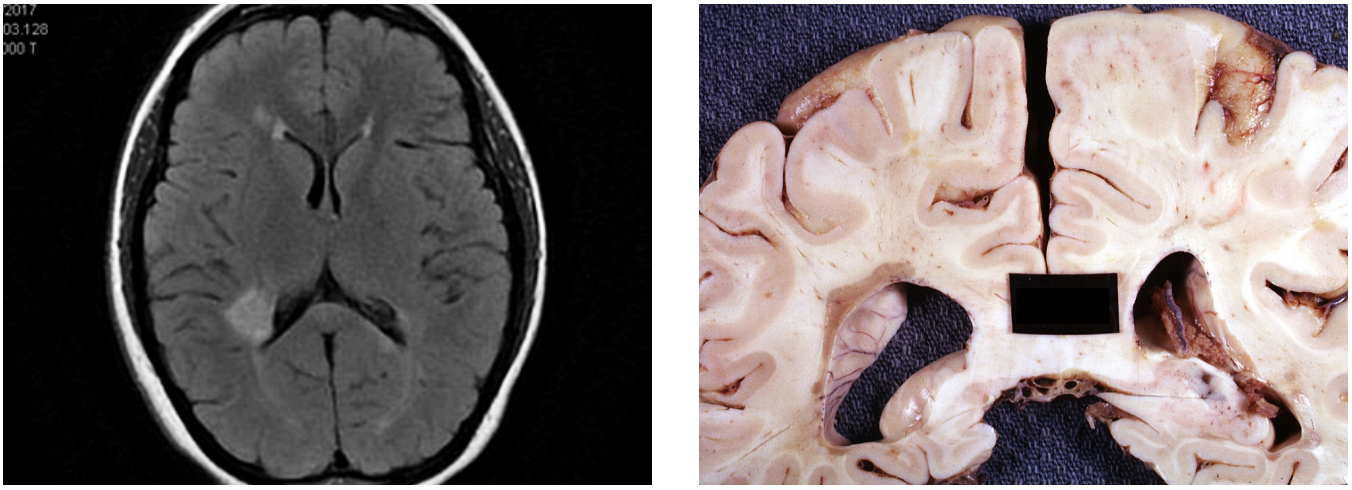


Figure 10.2: Internuclear Ophthalmoplegia (INO)
The lateral rectus muscle is innervated by cranial nerve (CN) VI on the ipsilateral side, and the medial rectus muscle is innervated by CN III on the ipsilateral side. The medial lateral fasciculus (MLF) connects CN VI to the contralateral CN III. (a) Normally, when you look left, CN VI on the left tells both the left eye's lateral rectus muscle and the right eye's medial rectus muscle to contract—both eyes move left. (b) When there is loss of the MLF and you look left, the left eye's lateral rectus still functions, but the right eye's medial rectus does not receive a signal and fails. The left eye moves left, but the right eye is unable to pass the midline, resulting in blurry vision.

The best diagnostic modality for MS is radiography. An **MRI with contrast** of the brain and spinal cord will show **bright white lesions** from inflammation in the affected regions. A radiographic description of **periventricular white matter** is a board favorite. But, be careful with the wording. Though the associated inflammation from an MS lesion causes a "white" appearance on imaging, the underlying loss of myelin causes a different change in color of the actual brain tissue as seen on pathologic specimen. Neurons and their axons are **grey matter**, while the insulation around those axons, **myelin**, **is white matter**. Axons that have lost their myelin sheath will look grey on examination, like the rest of the neurons.

Though not usually needed for diagnosis of MS, a lumbar puncture may be done during the workup and has distinct features you must know: **lymphocytes**, **oligoclonal IgG bands**, and **myelin protein**. This makes sense, as MS is an autoimmune disease, causing IgG to attack myelin.

Acute MS flares are treated with steroids to reduce inflammation from new lesions. Chronic treatment of MS includes interferon as well as a host of other medications you do not yet need to know.



(a) (b)

Figure 10.3: Pathologic Findings of Multiple Sclerosis
(a) An MRI with contrast revealing periventricular white plaques. The contrast is used to enhance the areas of inflammation, causing the white appearance on imaging. (b) Gross pathologic examination of a brain affected by MS reveals loss of white matter, which instead appears more grey. This is due to loss of the white myelin sheath.

Guillain-Barré

Guillain-Barré is an **autoimmune disease** that causes **demyelination** within the peripheral nervous system. Antibodies develop against the peripheral nervous system's version of myelin, the **Schwann cells**. The longest nerves are affected first, causing a classic **ascending paralysis** which can, in some severe cases, cause **paralysis of the diaphragm**, leading to respiratory failure and death. Often, the patient experiences a preceding viral illness (e.g., *Campylobacter* causing diarrhea, *influenzae* causing myalgias) or vaccination two weeks before the paralysis begins, and the course may be indolent, progressing slowly over days to weeks. Over time, the paralysis will completely reverse.

Myasthenia Gravis

Myasthenia gravis is an **autoimmune disorder** caused by **antibodies against postsynaptic nicotinic ACh receptors**. Binding of these antibodies to the receptor does **not activate them**, but rather competitively inhibits acetylcholine from being able to bind. This **competitive inhibition** can be overcome by increased levels of acetylcholine in the synaptic cleft.

However, **it takes time** for the presynaptic neuron to make more ACh available for release. At rest, the neuron is busy building ACh, packaging it into vesicles, and shuttling those vesicles to the NMJ in order to make it available for release. When the human instructs her arm to move, it moves. At the first attempt at contraction, there are the maximum number of vesicles prepared to launch. If she attempts to contract again, the impulse travels without difficulty to her endplate, but if there wasn't sufficient time to replenish all the vesicles, this next contraction is weaker, with less ACh released. With less ACh released, it also means there's less to compete with the inhibitor. On repeated contraction, the muscle force gets weaker and weaker, as presynaptic neurons are depleted of ACh vesicles, and the antibodies win. If she rests, the vesicles are restored, and the next contraction is strong again.

Thus, the classic finding in MG is a **decaying force of contraction on rapidly repeated contractions**. It follows that **small muscles** and/or those **that get used a lot** are going to be affected the most. Patients will complain of **blurry vision** (the eye muscles), dysphagia (the esophagus), and **difficulty writing** (the hands).

Patients with MG sometimes have a hyperproliferation of mediastinal thymic tissue, a thymoma, which must be looked for with a CT scan. If present, removal of a thymoma can reverse symptoms of MG. MG is also treated by giving the endplate a boost—providing ACh-esterase inhibitors to prevent slow degradation of ACh at the synaptic cleft.

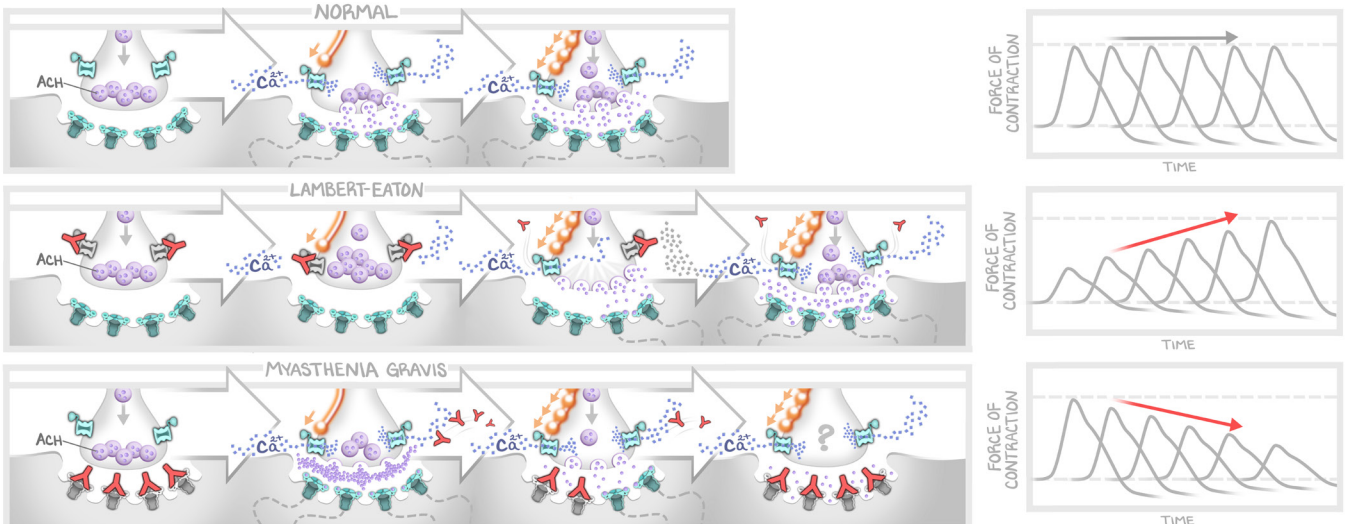


Figure 10.4: Myasthenia Gravis and Lambert-Eaton
(a) At a normal NMJ, all attempted contractions generate equal force. (b) In L-E, the presynaptic channels are blocked, preventing a single depolarization from causing sufficient ACh release. But, after subsequent attempts, the repeat depolarizations displace the Ab, allowing subsequent contractions to gain contractile strength. (c) In MG, the first contraction, relying on premade vesicles, is normal. But subsequent attempts require more ACh than normal, and ACh can't be regenerated fast enough, so there is decay in force of the repeated contractions.

Lambert-Eaton

Lambert-Eaton is a **paraneoplastic syndrome** associated with **antibodies** to **presynaptic calcium channels**. When an action potential arrives at the presynaptic terminal, voltage-gated calcium channels open. The **influx of calcium** causes exocytosis of the vesicles filled with ACh, flooding the synaptic cleft with ACh that then activates the postsynaptic receptors to cause a muscle contraction. The antibodies to the calcium channels makes it hard to have the first contraction, as one action potential is not enough to **open the blocked channels**. But, with repeated stimuli, the action potentials add together to open enough calcium channels to achieve the normal contraction. Thus, **increasing the frequency of contraction increases the strength of contraction**. Muscles we don't use often get affected first, so patients classically present with **painless proximal muscle weakness**. They may describe difficulty climbing stairs, rising from a chair, or brushing their hair.

This paraneoplastic syndrome is almost always associated with small cell carcinoma of the lung. Treatment of the cancer usually reverses the symptoms.

Citations

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